The Cardiovascular and Renal Advisory Panel of the Food and Drug Administration (FDA) met to discuss the safety and effectiveness of the antiarrhythmic agent dofetilide and the natriuretic peptide nesiritide.

**Dofetilide (Tikosyn)**

Dofetilide is a class III antiarrhythmic agent that prolongs the effective refractory period by blocking a single type of potassium channel (IKr). Data were presented from 2 large efficacy trials and a mortality trial (Danish Investigation of Arrhythmia and Mortality ON Dofetilide [DIAMOND]) in support of a proposal to market an oral formulation of dofetilide for the conversion of chronic atrial fibrillation/flutter (AF) to normal sinus rhythm and for the maintenance of sinus rhythm once converted. Dofetilide was not effective in patients with paroxysmal AF or with paroxysmal supraventricular arrhythmias.

Study 345 enrolled 671 patients in Europe who had AF for 2 years. Study 120 enrolled 325 patients in North America who had a more recent onset of AF (2 weeks to 6 months). Three different doses (125 μg, 250 μg, and 500 μg) were compared with placebo. In these trials and in subsequent studies, doses were decreased if creatinine clearance was low or if the QT interval (averaged over 10 to 15 beats) was increased by 15%; after the initiation of therapy, all patients were monitored in the hospital for 3 days. In both large AF trials, dofetilide was superior to placebo at terminating AF within 3 days of therapy, especially at the 500-μg dose (30% versus 1.5%, P<0.001); however, with the addition of electrical cardioversion, restoration of sinus rhythm was similar in treatment and placebo groups (80%).

Dofetilide produced a dose-related increase in the proportion of patients maintaining sinus rhythm. Patients randomized to the 500-μg dose had the greatest efficacy at 1-year follow-up in studies 345 and 120 (66% versus 21%, P<0.0001, and 58% versus 25%, P=0.011, respectively, compared with placebo). The clinical benefit of maintaining sinus rhythm was not demonstrated in these trials, but panel members generally accepted a potential clinical benefit of not being in AF.

The DIAMOND study randomized 3028 high-risk patients with congestive heart failure or recent myocardial infarction to placebo or dofetilide; 17% had AF. At a median follow-up of 12 months, overall mortality was 36%, with no difference between dofetilide and placebo groups. A decrease in hospitalizations was observed in patients randomized to the drug, and the difference seemed largely attributable to a difference in the maintenance of sinus rhythm among patients entering the trial in AF.

The only significant adverse effect of the drug was a dose-dependent increase in QT intervals and torsade de pointes. Proarrhythmia was more common in female patients and in those with ventricular arrhythmias, heart failure, and concomitant digoxin or verapamil use. The incidence of torsade de pointes in the AF trials (120 and 345) was <1%, but it was higher (3.6%) in the heart failure patients in DIAMOND. Moreover, drug levels were increased in patients with a low body weight, those with moderate liver dysfunction, and those on other drugs (cimetidine, ketoconazole, verapamil, oral contraceptives, and thiazides).

The majority of the discussion centered on safety issues, such as the narrow therapeutic:toxic ratio, multiple drug interactions, difficulty in dosing with adjustments for creatinine clearance and QT intervals, the need for 3-day in-hospital monitoring, and the fact that drug levels are not commercially available. Despite these concerns, the committee felt that more safety data were available for dofetilide than most drugs currently used for AF. Therefore, in a split vote, it was recommended that dofetilide be approved for both conversion of chronic AF and maintenance of normal sinus rhythm.

**Nesiritide (Natrecor)**

Human B-type natriuretic peptides have vasodilatory, diuretic, natriuretic, and neurohormonal actions. Nesiritide is a purified peptide produced by recombinant DNA technology.
Data were presented in support of a proposal that intravenous nesiritide be approved for acutely decompensated congestive heart failure. On the basis of prior discussions with the FDA, the main goal of the studies was to identify the dose ranges of nesiritide that produced favorable hemodynamic effects.

Eight trials randomized 721 patients with severe congestive heart failure to placebo or a range of nesiritide doses. Nesiritide treatment was associated with significant decreases in pulmonary capillary wedge pressures and systemic vascular resistance with increases in cardiac index. This occurred in the absence of increases in heart rate. Treated patients experienced improved symptoms of dyspnea and fatigue. Some studies found that nesiritide was associated with sodium and water retention and decreased urine output. Although this may have been due to an imbalance in diuretic use, nesiritide-treated patients also experienced 3 cases of renal failure.

The discussion of the panel centered on safety issues, such as the effect of the drug on serum creatinine, bradycardia, and hypotension, which required drug discontinuation more often than current therapies (ie, dobutamine and nitroprusside). Hypotension occurred more commonly with the concomitant use of angiotensin-converting enzyme inhibitors, and no data were available regarding adverse effects in patients using nitrates and diuretics. Concern was also expressed over a lack of data in patients with either myocardial infarction or unstable angina and congestive heart failure. Moreover, it was not clear whether the assessment of symptoms was objective because the investigator knew the hemodynamic measurements. The panel also discussed the timing of the onset of effect, which seemed slower than with currently used intravenous therapies and thus seemed to preclude the conventionally-used approach of rapid dose-titration to a hemodynamic end point. Some studies used a bolus, but the data did not indicate that this appreciably shortened the time to onset of effect. Finally, there were discussions regarding whether the population tested was large enough or sick enough to ascertain the morbidity and mortality of nesiritide.

The panel voted 5 to 3 for approval, primarily on the basis of the acute hemodynamic benefit. However, many of those who voted “yes” reiterated the above safety issues and expressed a desire for additional studies to be undertaken. Moreover, a claim for a reduction in the symptoms of heart failure was not recommended. In part because of the issues raised in this discussion, nesiritide did not receive FDA approval.

References

Key Words: anti-arrhythmia agents ■ atrial flutter ■ atrial natriuretic factor ■ heart failure
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